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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,475	11/11/2003	Vincenzo Cerundolo	NY-LUD-5629-3-DIV	8208

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,475	CERUNDOLO ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/11/03, 12/15/03 and 5/17/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-58* is/are pending in the application.

4a) Of the above claim(s) *49-56 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 11/11/03 and 12/15/03 and Applicant's response filed 5/17/04 are acknowledged and have been entered.

2. Applicant's election with traverse of Group III (claim 57), and species of SEQ ID NO: 6 SLLMWITQA in Applicant's said response is acknowledged.

Claim 57 reads on the elected group and species, contrary to Applicant's assertion that claim 58 is readable thereon. Claim 58 belongs to non-elected Group IV.

The basis for the traversal is that there is allegedly no basis for the requirement for electing an *in vitro* vs an *in vivo* method of administration.

Applicant's arguments have been fully considered but are not persuasive. It is the Examiner's position that no requirement has been made in the restriction requirement mailed 4/20/04 for electing an *in vitro* vs an *in vivo* method of administration. It is the Examiner's position that Group III (claim 57) is drawn to a method comprising administering a fusion *protein* to a cell, whereas Group IV (claims 57 and 58) is drawn to a method comprising administering a *nucleic acid molecule* encoding a fusion protein to a cell.

The requirement is still deemed proper and is therefore made FINAL.

Claim 57 is currently being examined.

Accordingly, claims 49-56 and 58 (non-elected groups I, II and IV) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

3. Applicants are required under 37 C.F.R. 1.821(d):

a. to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 9 at Table 2).

b. to amend claim 57 to recite the SEQ ID NO after the sequence appearing in the said claim.

4. The amendment filed 11/11/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference to application serial no 09/514,036. The said amendment is not listed in the Declaration.

Applicant is required to cancel the new matter in the reply to this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 57 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method for facilitating delivery of a tumor rejection antigen (TRA) to an MHC molecule, the TRA peptide being of the formula of SEQ ID NO: 10 recited in the instant claim, comprising administering a fusion protein to a cell which is taken up by the said cell and cleaved thereby to form said peptide, followed by delivery of said peptide to said MHC molecule.

The instant claims encompass a method of delivering a peptide of SEQ ID NO: 10 to any MHC molecule, including those that are not HLA-A2 and including those that are not even class I MHC molecules. In addition, the instant claims encompass use of peptides that are not disclosed in the specification to bind to HLA-A2 and encompass the use of fusion proteins comprising any non SEQ ID NO: 10 portion that is not disclosed as enunciated below. There is insufficient disclosure in the specification on such a method.

The specification discloses that SEQ ID NO: 10 is a series of analogue peptides of the NY-ESO-1 peptide SLLMWITQC, wherein the "C" is replaced with one of A, V, L, I, P, F, M, W or G, and that the peptides ending in A, L or V were capable of binding to HLA-A2 and being recognized by ESO1 specific HLA-A2 restricted CTL (Tables 1 and 2, especially). The specification provides no disclosure that the peptides with I, P, F, M, W or G are able to bind to HLA-A2 (page 15 at the last 6 lines and continuing onto page 16 at lines 1-2). The specification discloses that D'Amaro et al and Drijfhout et al (page 5 at lines 1-7) provide the motif for peptides that bind to HLA-A2. However, D'Amaro et al and Drijfhout et al teach that the carboxy terminal amino acid residue may be A, C, I, L T or V. The specification further discloses that the fusion proteins may be comprised of additional tumor rejection antigens (TRAs), reporter proteins or peptides, protein or peptide segments that facilitate the

cleavage of the TRAs from the fusion peptide or protein, or proteins or peptides that facilitate the delivery of the TRAs to a relevant MHC molecule (page 17 at lines 2-22).

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any MHC molecule, SLLMWITQC analogues with carboxy terminal amino acid residues that may not bind to HLA-A2, and portions of fusion proteins that are not those portions enunciated above. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

7. Claim 57 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a method for facilitating delivery of a tumor rejection antigen to an MHC molecule, the TRA peptide being of the formula of SEQ ID NO: 10 recited in the instant claim, comprising administering a fusion protein to a cell which is taken up by the said cell and cleaved thereby to form said peptide, followed by delivery of said peptide to said MHC molecule.

The specification has not enabled the breadth of the claimed invention because the claims encompass a method of delivering a peptide of SEQ ID NO: 10 to any MHC molecule, including those that are not HLA-A2 and including those that are not even class I MHC molecules, in addition, the instant claims encompass use of peptides that are not disclosed to bind to HLA-A2 and the use of fusion proteins comprising any non SEQ ID NO: 10 portion that is not disclosed as enunciated below.

The specification discloses that SEQ ID NO: 10 is a series of analogue peptides of the NY-ESO-1 peptide SLLMWITQC, wherein the "C" is replaced with one of A, V, L, I, P, F, M, W or G and that the peptides ending in A, L or V were capable of binding to HLA-A2 and being recognized by ESO1 specific HLA-A2 restricted CTL (Tables 1 and 2, especially). The specification provides no disclosure that the peptides with I, P, F, M, W or G are able to bind to HLA-A2 (page 15 at the last 6 lines and continuing onto page 16 at lines 1-2). The specification discloses that D'Amaro et al and Drijfhout et al (page 5 at lines 1-7) provide the motif for peptides that bind to HLA-A2. The specification further discloses that the fusion proteins may be comprised of additional tumor rejection antigens (TRAs), reporter proteins or peptides, protein or peptide segments that facilitate the cleavage of the TRAs from the fusion peptide or protein, or proteins or peptides that facilitate the delivery of the TRAs to a relevant MHC molecule (page 17 at lines 2-22).

However, evidentiary references D'Amaro et al and Drijfhout et al teach that the carboxy terminal amino acid residue may be A, C, I, L T or V.

The specification does not disclose the claimed method using non-SEQ ID NO: 10 portions of a fusion protein that are not disclosed as enunciated above, nor working examples of SEQ ID NO: 10 analogue peptides binding to any MHC class I molecule except for HLA-A2, nor working examples of SEQ ID NO: 10 analogue peptides ending in P, F, M, W or G that bind to HLA-A2 or any MHC class I molecule, nor how to use such a peptide in the claimed method if it does not bind to HLA Class I.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 57 is rejected under 35 U.S.C. § 103(a) as being unpatentable over US 6,417,165 B1 in view of WO 99/14326.

US 6,417,165 B1 discloses peptide SLLMWITQA (SEQ ID NO: 6 of the instant application) is an analogue of the naturally occurring NY-ESO-1 peptide SLLMWITQC that exhibits dramatically enhanced binding to HLA-A2 and recognition by HLA-A2 restricted CTL compared with the naturally occurring peptide. US 6,417,165 B1 discloses that peptide SLLMWITQA is useful therapeutically or diagnostically for HLA-A2 positive patients who express NY-ESO-1 in connection with a pathology, including to determine if HLA-A2 positive cells are present, or if relevant CTLs are present. US 6,417,165 B1 further discloses that fusion proteins comprising the said peptide and/or other variant peptides can be constructed, and that the additional protein or peptide segments can be reporter proteins or peptides, proteins or peptides that facilitate the cleavage of the TRA peptide (or the analogue such as SEQ ID NO: 6) from the fusion protein, or that facilitate the delivery of the TRA peptide or analogue to a relevant MHC molecule, or can be used with other peptides in polytope peptides or proteins. (especially abstract, Table 1, Example 8 and claims). US 6,417,165 B1 discloses delivery of the fusion proteins to cells via introduction of nucleic acid molecules encoding the fusion proteins.

US 6,417,165 B1 does not disclose wherein the fusion proteins are administered directly to a cell, i.e., not as nucleic acid molecules encoding them.

WO 99/14326 teaches making fusion peptides or proteins comprising the naturally occurring NY-ESO-1 peptide SLLMWITQC and class II MHC binding peptides to stimulate CTL and $CD4^+$ T helper cells, respectively. WO 99/14326 teaches administering the fusion proteins or peptides in a standard administration protocol to animals to test the effectiveness of the polytope in stimulating, enhancing and/or provoking an immune response. WO 99/14326 teaches that the polytopes consisting of both MHC class I and class II binding epitomes are processed to yield individual epitomes that are presented by MHC molecules and recognized by CTLs (especially pages 27-29).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made and administered a fusion protein comprising the analogue peptide SLLMWITQA taught by US 6,417,165 B1, including as a polytope such as those disclosed by US 6,417,165 B1 or by WO 99/14326 to a cell directly as taught by WO 99/14326.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to get an enhanced immune response to NY-ESO-1 as taught by US 6,417,165 B1 and by WO 99/14326 for eliciting both arms of the cellular immune response.

10. Claim 57 is rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/14464 in view of Drifthout et al (Human Immunol. 43: 1-12, 1993), Thompson et al (J. Immunol. 157: 822-826, 1996) and Rammensee et al (Immunogenetics, 41: 178-228, 1995).

WO 98/14464 teaches peptides from NY-ESO-1 that are nonamers, decamers or undecamers having a core sequence of LLMWIT and having Serine before the first Leucine, and 0-4 additional amino acid residues C-terminal to the Threonine, which bind to HLA-A2 molecules. WO 98/14464 further teaches that the peptides may be used therapeutically with an adjuvant and/or additional peptides, i.e., in a pharmaceutical preparation administered to a patient, to provoke a CTL response or may be used in vitro to stimulate CTL for administration to a patient (especially page 21 at lines 26-37, page 22 at lines 1-3 and claims 27-32 and page 19). WO 98/14464 teaches a peptide SLLMWITQC from NY-ESO-1 that stimulates an HLA-A2 restricted CTL line (especially pages 16 and 17 at example 11). WO 98/14464 teaches peptides that complex with an MHC class I molecule to generate CTL against abnormal cells, and that NY-ESO-1 is expressed in various cancers including melanoma and breast cancer (especially pages 8-10). WO 98/14464 teaches typing a patient whose cancer cells express NY-ESO-1 for HLA class I type and identifying peptides from NY-ESO-1 protein that bind to the relevant class I molecules (especially Example 11). WO 98/14464 teaches administering one or more peptides that bind to an HLA molecule on the surface of a patient's tumor cells in an amount sufficient to bind to the MHC class I molecules (especially page 19). WO 98/14464 teaches the motif for binding to HLA-A2 molecules.

WO 98/14464 does not teach the nonamer peptide SLLMWITQA (SEQ ID NO: 6 of the instant application), nor method of administration of a fusion protein comprising the peptide.

Drijfhout et al teach oxidative dimerization of peptides with Cys at the carboxy-terminus, and that such dimerization is undesirable for peptide binding (especially page 9, column 1). Drijfhout et al further teach that the carboxy terminal amino acid residue may be an "A" in nonamer peptides (especially page 8 at the first full paragraph at column 1).

Thompson et al teach the superiority of polytopes, i.e., fusion peptides or proteins, comprising at least 10 contiguous minimal CTL epitopes for delivery to tumor cells. Thompson et al further teach that every CTL epitope is processed and presented. Thompson et al teach the efficacy of the polytope approach in spanning the HLA diversity of the population.

Rammensee et al teach motifs for peptides that bind to many different class I or class II MHC molecules and method of screening for peptides that bind to the said class I or class II MHC molecules.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a nonamer analogue peptide with the sequence SLLMWITQA given the teaching of WO 98/14464 of an antigenic 9-mer peptide SLLMWITQC from NY-ESO-1 that binds to HLA-A2.1 and stimulates an HLA-A2 restricted CTL line, and given the teaching of Drijfthout et al that the presence of Cys at the carboxy-terminus of a peptide is undesirable for peptide binding to class I molecules and of the motif for nonamer peptides that bind to the HLA-A2 class I molecule include "A" at the carboxy terminus. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made a fusion protein comprising SLLMWITQA and comprising additional peptides, given the teaching of Thompson that polytope peptides or proteins are superior in generating CTL responses, particularly in HLA diverse populations, and the teaching of WO 98/14464 that peptides from NY-ESO-1 protein that complex with HLA class I molecules are useful for generating CTL against abnormal cells, and the method of screening the said protein for subsequences that bind to a class I molecule, said screening method also taught by Rammensee et al for peptides that bind to many different class I or class II MHC molecules.

One of ordinary skill in the art at the time the invention was made would have done this in order to construct a more efficient analogue peptide and fusion protein comprising the said peptide for treatment of HLA-A2 NY-ESO-1 positive patients and other patients.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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